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| 09/844,517 | 04/27/2001 | Erich Hoffmann | 2427/1G772-US1 | 9063 |

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| EXAMINER |
|---|
| HILL, MYRON G |

| ART UNIT | PAPER NUMBER |
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| 1648 | |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/844,517 | HOFFMANN, ERICH | |
| | Examiner | Art Unit | |
| | Myron G. Hill | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on *10 February 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1- 32,39, and 42- 45* is/are pending in the application.

4a) Of the above claim(s) *1- 14, 42, and 43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15- 32,39, and 44- 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *19*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

This action is in response to Amendment B, filed 10 February 2003.

Upon further consideration Invention I is not rejoined. As indicated in the prior Office action, the claims *could* be rejoined; however, until allowable subject matter is determined in the pending claims the claims of group I will remain withdrawn.

Claims 1- 14, 33- 38, 40, and 41- 43 are withdrawn from further consideration.

Claims 15- 32, 39, 44, and 45 are under consideration.

### *Rejections Withdrawn*

### *Claim Rejections - 35 USC § 112*

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 15- 32, and 39 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The amendments and arguments overcome the rejections the rejections of record; however, see new rejections below.

The rejection of claims 15- 32, and 39 for 112, first paragraph, deposit requirement is withdrawn.

***Rejections Maintained***

***Claim Rejections - 35 USC § 112***

Claims 15- 32, 39, 44,and 45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for production of influenza viruses, does not reasonably provide enablement for the full range of negative stranded viruses. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The claims are drawn to a minimum plasmid rescue system for any segmented negative stranded virus.

Applicant argues that the specification discloses specific systems for other negative strand viruses, including parainfluenza, Reoviridae, Bunyaviridae, and others (response, page 12, top). Then Applicant details several reports of negative stranded viruses that have had reverse genetic systems or rescue reported and the passage of Hoffman and Webster from J Gen Virology, page 2846. That Examiner has failed to provide any examples for reasons of non-enablement [MPEP and case law citations omitted]. Then lists a number of recently published works providing proof of enablement.

Applicant's arguments have been fully considered and found persuasive in part.

First, as to the case law and MPEP, Examiner is not always required to cite specific art but specific technical reasons are always required. One of skill in the art knows that expression of more than protein is required for rescue of non-segmented

negative strand viruses and Applicant has not shown or provided a reason why a one plasmid based system would work. The cited art by Applicant for enablement is not commensurate with the claims as now written. The cited art either suggests such would work (influenza C) or is drawn to systems that are not minimum plasmid based to produce virus (THOV of Wagner). It is clear that all the cited examples are not commensurate with the claims. Thus, the full scope of the claims is not enabled.

Applicant has shown the system will work with influenza A and B. The art citing cytoplasmic function of the transcripts is only convincing to the extent that it works with each specific virus because Pekosz (page 8806, column 1, last sentence of first full paragraph) teaches that because of mRNA splicing in the nucleus, the successful use of the POLI system with other viruses will depend on absence of cryptic splicing signals in the viral transcripts. This indicates that every virus must be tested to see if it contains cryptic splice signals. Thus, the range of segmented negative stranded viruses that can be rescued cannot be known until each one is tested.

***Claim Rejections - 35 USC § 103***

Claims 15- 32, 39, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoffmann (Dissertation in translation,1997, from IDS) and Neumann (PNAS, 1999 in IDS).

Applicant argues that there is no suggestion to combine, that Neumann does not use a POLI POLII plasmid, that Hofmann uses helper virus, Hoffmann does not rescue virus, and only uses the POLI-POLII plasmid to express a reporter gene, the plasmids of

Hoffmann include up mutations which are down mutations in other systems, the over expression of certain influenza genes results in low reporter activity, the invention results in increased commercial success, that Neumann teaches using more plasmids and teaches away from using less plasmids and a POL I –POL II plasmid, and that Neumann did not come up with the system even though Hoffmann is co-author on several publications including Neumann cited here.

Applicant's arguments have been fully considered and not found persuasive.

Neumann's increased number of plasmids are needed to express additional viral proteins to increase virus yield from transfection. The functional elements of the promoters used by Neumann are POLII to make mRNA and POLI to drive expression of genomic RNA on different plasmids.

Hoffmann teaches a plasmid that contains both promoters, POLI and POLII.

Pekosz teaches as is known in the art the complexity of transfection of up to 17 plasmids and the benefit of no helper virus. This would lead one of skill in the art to desire a helper free system that had fewer plasmids but the efficiency of the Neumann 17 plasmid result. The level of skill in the art is high as evidenced by the publications cited by Applicant. Hoffmann provides an answer to this problem by providing one plasmid that can act as both mRNA and genomic RNA. One of ordinary skill in the art would see this would result in a reduction in the number of plasmids that would be required to transfect in the system of Neumann.

Applicant argues that the plasmid of Hoffmann has to be combined with helper virus. It is noted that the plasmid of Hoffmann is active in cells without helper virus

(page 115, lines 9- 12) as shown by the disclosure that CAT activity was detected in the absence of helper virus. This indicates that the plasmid was able to make mRNA and then protein of the synthetic message. Additionally as noted in the rejection of record, that the CAT-influenza segment can be passaged onto cells without helper virus and CAT activity can still be detected. This shows that the CAT-influenza segment has the correct ends to be replicated and packaged in the virion which can function in the absence of helper virus. The plasmid of Hoffmann does not require helper virus.

Applicant asserts that the plasmids of Hoffmann contain mutations that result in a promoter down effect. Not all the clones of Hoffmann use regulatory sequence mutations. Applicant cites Figure 3-4 on page 56 which teaches a study of mutations at the end of gene segments in a system that used POLI expression plasmids, which is in a different section than that referred to by the Examiner. Applicant is in error when stating that Figure 3-4 uses the POLI-POLII system. The section referred to by the Examiner does not use that system but the POLI-POLII plasmids. See Figure 3-44 (page 116) which uses the ends of segment 5 of influenza in a POLI-POLII plasmid.

Applicant also asserts that over expression causes reduction of reporter as evidenced by at least Gomez-Puertas. The plasmid system used is not the same as the claims. Furthermore, Figure 1 discloses an optimization of plasmids for the Gomez-Puertas system. Optimization is routine laboratory work. Applicant points to this and Neumann to indicate that this teaches away from using a POLI-POLII plasmid system because "the use of this [POLI-POLII plasmids] does not assume achieving unequal

levels of expression proteins." It is not clear what this means. The Examiner interprets it to mean that it is assumed that this system cannot achieve unequal amounts of protein expression. This is not found persuasive because the prior art does not teach the POLI-POLII plasmids cannot be optimized and those cited references teach optimization, not that plasmid expression systems fail.

Applicant on page 22, middle, argues that Hoffmann while presenting a "very interesting scientific story" does not provide the expectation of success for achieving the "difficult" goal of reconstituting infectious virus. It is clear from the results discussed above as to the CAT activity produced from the interesting scientific story, that the plasmid of Hoffmann is able to function to make mRNA and genomic RNA.

Applicant is correct in stating that Neumann did not use the plasmid of Hoffmann. The fact that Neumann did not use the plasmid of Hoffmann, even though they were co-authors, is not an issue that can be solved from the prior art of record. As discussed above, Applicant's argument that the prior art teaches away from POLI-POLII plasmids is not persuasive and the Office without additional information regarding what Neumann knew and tried cannot determine the use or lack thereof in the prior art. Additionally, it is not what Neumann did or did not do, but what one of ordinary skill in the art would think knowing Hoffmann and Neumann.

The commercial success has not been fully demonstrated by the abstract submitted because it only suggests that the method can be used to make vaccine virus. Commercial success requires at least success in the marketplace, a nexus between success and the marketplace, and success is based on inventive aspects not just

marketing. Furthermore, both (Hoffmann and Neumann) use A/PR/8/34 as a backbone for rescued virus and it would be expected that both would grow to the same titers when both are amplified in eggs. As far as the Graham citation is concerned, long felt need is not an issue because influenza vaccines are in wide use.

### *New Rejections*

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15- 32, 39, and 44- 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The system as written in claim 15 is a product claim of a set of plasmids. The elected group is drawn to production of virus, class 435, a method. Claims 29- 32 and 39 are drawn to methods which depend from plasmids and host cells that contain the plasmids. Claims 15- 28, 44, and 45 recite a system for the generation of infectious segmented negative strand viruses but contain no active method steps that result in the production of infectious virus.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 15- 32, and 39 are rejected under 35 U.S.C. 102(a) as being anticipated by Hoffmann et al.

Hoffmann et al. disclose the invention as claimed.

They disclose a minimum plasmid based system (8 plasmids) to generate infectious segmented negative stranded RNA viruses from cloned viral cDNA (see entire document).

***Claim Rejections - 35 USC § 103***

Claim 45 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hoffmann and Neumann as applied to claims 15- 32, 39, and 44 above, and further in view of Pleschka.

Hoffmann and Neumann teach a system to produce infectious influenza virus with 8 plasmids. As recognized by them and as known by one of ordinary skill in the art, there is a need for precise ends on influenza genomic RNA segments. Hoffmann and Neumann teach use of a polymerase terminator.

Pleschka teaches that ribozymes can be used to generate specific ends of influenza segments (see at least Figure 1).

Ribozymes both hammerhead and HDV are well known in the art as shown by Pleschka. One of ordinary skill in the art at the time of the invention would have known that ribozymes function to produce specific ends of on RNA molecules.

Thus it would have been prima facie obvious to substitute a ribozyme with a terminator in a plasmid used for the production of influenza vRNA with the expectation of success.

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Myron G. Hill whose telephone number is 703-308-4521. The examiner can normally be reached on 9am-6pm Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4247. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Myron G. Hill
Patent Examiner
August 8, 2003

JAMES HOUSEL 8/8/03
SUPERVISORY PATENT EXAMINER
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